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Spray drying and post-processing production of highly-porous lactose particles using sugars as templating agents

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ABSTRACT

The possibility of using different carbohydrate sugars, such as maltose, sucrose, glucose, and fructose, as templating agents to produce highly-porous lactose particles with high degrees of crystallinity in a new templating process has been investigated. The new production process includes spray drying of the lactose (core material) solutions containing different types of ethanol-soluble templating sugars and then removing the templates in a post-treatment process involving ethanol-washing the spray-dried particles. Gravimetric moisture sorption tests and modulated scanning calorimetry (MDSC) have been used to study the effect of different concentrations of templating sugars on in-process crystallization of lactose during the spray-drying step and its effect on the BET surface areas of the final processed particles after ethanol washing. The results showed significant reductions in process yield and glass-transition temperatures of the spray-dried powders and considerable increases in the degree of crystallinity of the lactose in spray-dried powders, as the templating-sugar concentrations were increased. Spray-dried powders containing sucrose and maltose as templating materials had lower degrees of crystallinity, which resulted in higher porosities and BET surface areas of around 20 ± 1 and 18.2 ± 0.6 m^2/g, respectively. The results of this study have implications in choosing the proper processing conditions (type of templating agent and its concentration) to control in-process crystallization of lactose during spray-drying to produce highly-porous engineered particles.

1. Introduction

Spray drying is a convenient one-step process for particle production, but controlling the surface area, roughness, and porosity of the resulting particles is often challenging. Increasing the surface roughness and porosity of spray-dried particles significantly affects the compactability, tableting behavior, and dissolution rates of the powders, which has applications in food and pharmaceutical formulations [1–5]. Surface asperities improve bonding mechanisms between solid surfaces in a compact agglomerate, leading to stronger tablets [2], and these asperities increase the rate of water intrusion for fast tablet disintegration and dissolution [6,7].

Amorphous particles are known to have greater surface areas and consequently higher dissolution rates than crystalline ones, making them apparently better carriers for poorly soluble drugs [8,9]. However, extreme instability and hygroscopicity of amorphous materials are major drawbacks that decrease the physical and chemical stability of amorphous products [10,11]. Hence, producing stable crystalline particles with high porosity and surface roughness is the best way to avoid problems associated with unstable amorphous particles. In our previous works [12–14], a new production method was proposed, based on a templating concept [15–18] for producing highly-porous lactose with a high degree of crystallinity using citric acid as a templating agent.

The proposed templating process includes spray drying the aqueous solutions of water soluble materials, such as lactose and citric acid, to create a powder (of lactose and citric acid), and then washing the powder in ethanol to dissolve and remove the citric acid from the core lactose structure and simultaneously increasing the crystallinity of the spray-dried lactose. The processed powder is a highly-crystalline lactose network with significant porosity and high surface area and also high stability. The new templating method has also been successfully applied to produce high porosity mannitol particles using citric acid as a benign and non-toxic templating material [19].

It has been found in our previous studies [12,14] that lactose crystallinity in spray-dried particles increases as the pH of the solution decreases and the acidity increases, which has also been suggested by other researchers [20–22]. The lower BET surface areas for the processed particles from ethanol washing of the spray-dried powders at higher citric acid concentrations, and consequently higher degrees of crystallinity, suggested that increasing the lactose crystallinity in the spray-dried powders may have a negative effect on the BET surface areas of the processed powders after ethanol treatment [12]. Citric acid also significantly decreases the yield of the spray-drying process due to an increase in stickiness resulting from its low glass-transition temperature (T_g), so the addition of surface-active material, such as

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whey protein isolate (WPI), for recovery improvement was necessary [12]. Hence, the search for non-acidic templating materials that have minimum effects on the lactose crystallinity and the yield of the spray-drying process is highly desirable.

The main objective of this work is to study the possibility of using carbohydrate sugars, such as maltose, sucrose, glucose, and fructose, as non-acidic templates. These sugars have been commonly used in the food industry and also as excipients in drug delivery for pharmaceutical applications. The innovative aspect of this research is using non-acidic and food-grade sugars with similar natures to lactose as an alternative template to citric acid which has negative effects on the degrees of lactose crystallinity, BET surface areas, and process yields.

2. Materials and methods

2.1. Sample preparation

Pure α-lactose monohydrate crystals ($C_{12}H_{22}O_{11}.H_2O$; analytical reagent, Australia), D-maltose monohydrate ($C_{12}H_{24r}O_{12}$), sucrose ($C_{12}H_{22}O_{11}$), D-fructose ($C_6H_{12}O_6$), and D-glucose anhydrous ($C_6H_{12}O_6$) (laboratory-grade reagent, Australia) were used in this study. The experiments were carried out by varying the templating material from 1% to 5% (*w*/*w*) of the aqueous solution, with the lactose concentration kept constant at 10% (*w*/*w*). All solutions were magnetically stirred at the room temperature of 25 °C for at least 30 min, so a clear solution was obtained without any visible crystals being present. The clear solutions were then spray dried. The pH of the solutions was measured with a pH electrode, InPro 3250 series (Mettler Toledo, M 300, Switzerland).

2.2. Operating conditions for spray drying

A Buchi-B290 Mini Spray Dryer with an inlet gas temperature of 150 °C, a main air flow rate of 38 m^3/h (aspirator setting of 100%), a pump rate of 8 mL/min (25% of the maximum rate), and a nozzle air flow rate of 470 L/h (40 on the nozzle rotameter scale) has been used to spray dry the solutions. All experiments were performed in triplicate. Freshly spray-dried powder was collected from a vessel at the bottom of a cyclone, and a portion of that powder has been treated with ethanol for 48 h at the room temperature of 25 °C to remove the templating agent. The final processed powder has been obtained after vacuum filtering, oven drying at 60 °C for 1 h, and crushing and grinding the dried filtrate as shown in Fig. 1. The freshly spray-dried and ethanol washed powders were immediately used for moisture content, gravimetric moisture analysis, and BET analytical tests. The rest of the powders were kept in sealed bags and in a refrigerator to be used for scanning electron microscope (SEM) and modulated scanning calorimetry (MDSC) tests afterwards.

3. Powder characterization

3.1. Moisture sorption and oven drying tests

Crystallization behavior has been studied with two repeat samples of the powders produced from spray drying. A mass of 1–2 g of the powder has been placed on a 10-cm-diameter borosilicate glass Petri dish with a nearly monolayer particle thickness. The mass change as a function of storage time has been recorded by computerized data-logging once per minute over a period of at least 6 h to reach a constant mass by using an analytical balance (±0.0001 g, Mettler Toledo, AB 204-S, Switzerland). The sample and the balance have been placed in a sealed box, where the relative humidity (70–75% RH) and the temperature (24.5–25 °C) have been kept constant using a saturated salt solution of sodium chloride and electric light bulbs, respectively. The end of the crystallization process has been determined by the point where the sorption curve reached a plateau region [12]. The free moisture content (dry basis) has been measured by weighing the sample before and after drying in a fan circulated oven (Labec, Australia) at 85 °C for 24 h.

3.2. BET surface area analysis

Surface areas and pore volumes (or pore size distribution) have been determined from N_2 adsorption isotherms, measured at the temperature of liquid N_2 (77 K) using a surface area analyzer (Quantachrome Autosorb-1). The surface area has been calculated from the Brunauer–Emmet–Teller (BET) equations, and the total pore volume has been calculated according to the Barrett-Joyner-Halenda (BJH) method. All samples have been outgassed at room temperature overnight prior to the measurements. The experiments have been repeated at least three times using fresh powder.

3.3. Modulated differential scanning calorimetry (MDSC)

The glass-transition and crystallization temperatures and also the heat of crystallization for the powders have been determined by modulated differential scanning calorimetry (MDSC). Samples for MDSC measurements have been prepared according to standard procedures using hermetically sealed pans. Four to six mg of sample has been used in each analysis. The samples have been heated from 5 °C to 250 °C using a ramp rate of 5 °C/min with a 1 °C modulated signal every 60 s using a modulated differential scanning calorimeter (TA Instruments Q1000).

3.4. Scanning electron microscope (SEM)

A scanning electron microscope has been used to observe the powders in terms of the surface and bulk structures. The samples have been prepared by placing a small amount of sample onto a carbon

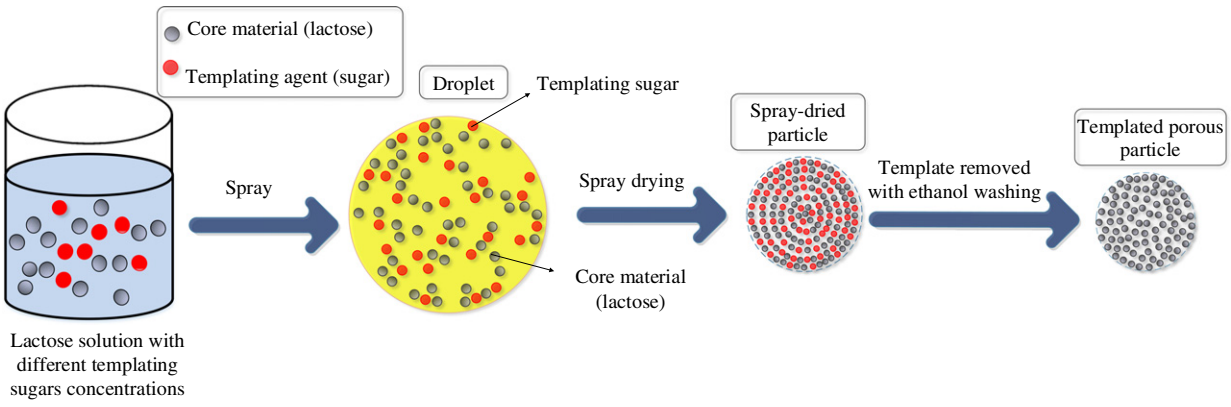

Fig. 1. Schematic diagram of the experimental arrangement and an illustration of the templating process.